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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 07/431,533
Filing Date: November 03, 1989
Appellant(s): MORTON ET AL.

Steven Highlander
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 21, 2000 appealing from the Office action mailed 06/21/2000.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 77

Application Number: 07/431533
Filing Date: November 3, 1989
Appellant(s): Donald MORTON et al.

Steven L. Highlander
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed November 21, 2000.

A statement identifying the real party in interest is contained in the brief.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existance of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

A. The 112, first paragraph, enablement rejection of claims 73-79 has been withdrawn.

B. Only claims 19, 62, 65 and 73-79 are rejected under 112, second paragraph. The rejection of claims 63, 64, 66-72 under 112, second paragraph has been withdrawn.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the claimed levels of purity of the claimed Urinary Tumor Associated Antigen (UTAA) are obvious in view of secondary references.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Euhus, D. Et al. "Demonstration and isolation of a glycoprotein tumor associated antigen from sera of melanoma patients." Proceedings of American Society of Clinical Oncology, vol. 7 (March 1988), p.44, abstract no. 169.

Exley, A.R. et al. "Optimal collection of blood samples for the measurement of tumor necrosis factor alpha." Cytokine, vol. 2, no. 5 (Sept. 1990), pp. 353-356.

Rote, N.S. et al. "Tumor-associated antigens detected by autologous sera in urine of patients with solid neoplasms". Journal of Surgical Research, vol. 29 (1980), pp. 18-22.

Finck, S.J. et al. "Excretion of tumor-associated antigen(s) in the urine of patients with colon carcinoma". Journal of Surgical Oncology, vol. 21 (1982), pp. 81-86.

Gel filtrarion, Theory and practice, (Pharmacia Fine Chemicals, 1980), pp. 4, 14, 26-27.

Ion exchange chromatography, Principles and methods (Pharmacia Fine Chemicals, 1980), pp. 3-7, 43-47.

Ljungquist, S. "A new endonuclease from Escherichia coli acting at apurinic sites in DNA". The Journal of Biological Chemistry, vol. 252, no. 9 (May 10, 1977), pp. 2808-2814.

Hofmann, HD. Et al. "Characterization and partial purification of a novel neurotrophic factor from bovine seminal vesicle". Journal of Neurochemistry, vol. 48, no. 5 (1987), pp. 1425-1433.

US, 4,348,376 GOLDENBERG 9-1982

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A. REJECTION UNDER 35 U.S.C. 101, OBVIOUSNESS-TYPE DOUBLE-PATENTING

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19, 62-66, 69-70, 72-79 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17, 48-60 of copending application Serial No. 08/462,570. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims 19, 62-66, 69-70, 72-79 in the present application are drawn to an antigen composition comprising UTAA, and a method for inducing or enhancing the production of antibodies reactive to UTAA comprising administering UTAA, whereas the claims 14-17, 48-60 are drawn to an antigen composition comprising UTAA, GM-2, GD-2, fetal antigen, and MTAA, and a mixture of tumor cells, and a method for inducing or enhancing the production of antibodies reactive to UTAA comprising administering UTAA, and at least one tumor associated antigen selected from the group consisting of GM-2, GD-2, fetal antigen, or MTAA. The claims 19, 62-66, 69-70, 72-79 in the present application and 14-

17, 48-60 in the application SN 08/462,570 are both drawn to the same antigen UTAA, and the same method of producing antibodies reactive to UTAA, and accordingly, are obvious variants. This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Therefore, the inventions as claimed are co-extensive.

B. REJECTION UNDER 35 U.S.C. 112, SECOND PARAGRAPH

Claims 19, 62, 65 and 73-79 are rejected under 35 U.S.C. 112, second paragraph.

Claims 19, 62, 65 and 73-79 are indefinite because claims 62 and 73 recite the language "substantially", which does not set forth the metes and bounds of the patent protection desired. The term "substantially" in the claims is a relative term which renders the claims indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

C. REJECTION UNDER 35 U.S.C. 103

Claims 19, 62-66, 69-70, and 72-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Euhus et al, in view of Exley et al, Rote et al, or Finck et al, Pharmacia Fine Chemicals, Gel filtration, Theory and practice, Pharmacia fine Chemicals, Ion exchange chromatography, Principles and methods, Ljungquist, S, US 4,348,376, further in view of Hofmann et al.

Claims 19, 62-66, 69-70, and 72-79 are drawn to an isolated Urinary Tumor Associated Antigen (UTAA) subunit, which after reduction by beta-mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis (SDS-PAGE), exhibits a molecular weight of about 90 to 100 kD, wherein said subunit contains glycosidase-sensitive carbohydrates, is heat stable at 100^0 C and has an isoelectric point of about 6.1. Said UTAA is purified at least about 100-fold, or 105-fold over UTAA found in urine, and is present as at least about 0.6% of total protein in the original composition. The claims 69-70 are further drawn to the claimed UTAA, which is about 95% or 99.5% free of immunoglobulin. Claims 19, 62-66, 69-70, and 72-79 are also drawn to a pharmaceutical composition comprising said purified UTAA, and a pharmaceutical buffer, wherein said UTAA is present as at least about 0.63 ug/ml, or 1.4 ug/ml, or 36 ug/ml, or 40 ug/ml, or 100 ug/ml, or 200 ug/ml of buffer. Claims 19, 62-66, 69-70, and 72-79 are further drawn to a method for inducing or enhancing in a subject the production of antibodies reactive with UTAA, comprising administering said purified UTAA. The observed enhancement of antibody production is about 2- to 5-fold.

Claims 73-79 recite the claimed UTAA, formulated as a pharmaceutical composition. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claims 73-79 read on the ingredient *per se*, which is UTAA.

Euhus et al. teach the isolation of urinary tumor asssociated antigen (U-TAA) from sera of melanoma patients. Euhus et al. also teach that because said antigen was detected in the urine of

melanoma patients, using autologous and allogeneic antibody in ELISA, it was termed urinary tumor asssociated antigen . A monoclonal antibody to U-TAA is developed, and used in ELISA to detect U-TAA. Said U-TAA is isolated by dye ligand, and gel filtration chromatography, and DEAE anion exchange chromatography or 4.5% polyethylene glycol precipitation. The free U-TAA in serum has a molecular mass of 620 kD, which is separated into four bands in SDS-PAGE; two of which, 142 kD and 111 kD, correspond to those present in U-TAA in urine. The isolated U-TAA is free of IgG and IgM. Euhus et al. further teach that pure U-TAA antigen will provide valuable reagents for the immunoprognosis of human melanoma.

Euhus et al. do not teach that UTAA contains glycosidase-sensitive carbohydrates, is heat stable at 100^0 C and has an isoelectric point of about 6.1. Euhus et al. do not teach that UTAA is purified at least about 100-fold, or 105-fold over UTAA found in urine, and is present as at least about 0.6% of total protein in the original composition. Euhus et al. do not teach that said UTAA is about 95% or 99.5% free of immunoglobulin. Euhus et al. do not teach a pharmaceutical composition, wherein said UTAA is present as at least about 0.63 ug/ml, or 1.4 ug/ml, or 36 ug/ml, or 40 ug/ml, or 100 ug/ml, or 200 ug/ml of buffer. Euhus et al. do not teach a method for inducing or enhancing in a subject the production of antibodies reactive with UTAA, comprising administering said purified UTAA, wherein the observed enhancement of antibody production is about 2- to 5-fold.

Exley et al teach how to perform enzyme-linked immunosorbent assay or ELISA.

Rote et al. teach tumor-associated antigens detected by autologus sera in urine of patients with solids neoplasms, using complement fixation assay. Unlike other tumor-related urinary antigens, the antigens taught by Rote et al induce a complement fixing antibody in the host, are heat stable at 100^0 C for 60 min. Said antigens are comprised of molecules of about $1x\ 10^6$ daltons, which could be dissociated into smaller subunits by treatment with 6 M urea.

Finck et al teach tumor-associated antigens found in urine of patient with colon carcinoma. Said antigen could be detected with complement fixation assay, using autologous serum as the antibody source. Said antigen has a molecular weight of >100,000 dalton, and is heat stable at 100^0 C (p.85).

Pharmacia Fine Chemicals teach how to purify proteins using gel filtration and ion exchange chromatography. Pharmacia teaches that "the separation of proteins in gel filtration depends on the different abilities of the various sample molecules to enter pores which contain the stationary phase. Very large molecules which never enter the stationary phase, move through the chromatographic bed fastest" Smaller molecules are eluted in order of decreasing molecular size" (Gel filtration, page 4). The eluent is just a simple buffer solution, as shown in one example on figure 6, page 14 (Gel filtration). Furthermore, molecular weight standards are routinely used for calibrating the gel filtration column (Gel filtration, pages 26-27). It is well known in the art that molecular weight standards could be easily tagged with dye ligands for color detection on the column. Pharmacia also teaches methods of elution of proteins from ion exchange columns, including DEAE columns, using a continuous NaCL gradient (Ion exchange chromatography,

pages 3-7, 43-47). Peaks of different proteins are separated by said continuous gradient elution, and thus could be detected.

Ljunquist teaches the purification of endonuclease IV by 3000-fold, using a combination of ammonium sulfate, gel filtration on Sephadex G-75, heat treatment, and DNA-cellulose.

US 4,348,376 teaches production of antibodies to the tumor antigen CEA, and the use of said antibodies for tumor localization and therapy.

Hofmann et al teach isolation of a protein, a neuronotrophic factor, using a combination of gel filtration method, preparative isoelectric focusing, and SDS-PAGE, wherein the protein is electrophoretically eluted from gel strips of SDS-PAGE (p.1427). The position of the gel strips could be determined by molecular weight standards. Using SDS-PAGE technique, the seminal vesicle-derived neuronotrophic factor (SVNF) could be completely separated from a closely associated protein, a nerve growth factor (NGF).

The art establishes that it was possible at the time the invention was made to isolate UTAA from sera of melanoma patients. Said UTAA is termed urinary tumor associated antigen because it is detected in urine of melanoma patients. A subunit of said UTAA from sera is 111 kD in SDS-PAGE, corresponding those present in UTAA in urine. Although 111 kD is not 90 to 100 kD, it is well known in the art that molecular weight determination by SDS-PAGE, at high molecular weight range, is not very accurate, and could easily vary by 10%. As also shown by applicant's own data, the molecular weight of the claimed UTAA varies by about 10%. Thus the 111 kD UTAA taught by Euhus et al. could have a similar molecular weight as the claimed

UTAA. The art also teaches the protocols for isolating UTAA, i.e. by gel filtration, and DEAE anion exchange columns, and elution of proteins from SDS-PAGE. Although the abstract by Euhus et al does not describe in detail how to isolate UTAA using gel filtration, and DEAE anion exchange columns, it is a routine protocol in the art, as shown in the handbooks Pharmacia, or Ljungquist. In other words, proteins of different sizes are separated by gel filtration, using a simple buffer solution; and different proteins are separated by a DEAE column, eluted as different protein peaks, using a continuous salt gradient elution. In addition, the art teaches how to isolate proteins from gel slices of SDS-PAGE, wherein the molecular weight of the gel slice could be determined by molecular weight standards in adjacent lanes. The art further teaches how to detect UTAA, i.e. either by ELISA, or by complement fixation test, using autologous or allogeneic sera of melanoma patients. Although the abstract by Euhus et al does not describe in detail how to perform ELISA, ELISA is a routine protocol in the art, as shown by Exley et al. Thus the eluted peaks from gel filtration, DEAE column, or gel slices of SDS-PAGE could be detected by either ELISA or by complement fixation test, using autologous or allogeneic sera of melanoma patients.

Therefore, it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to purify UTAA from urine or serum samples of melanoma patients, using the purification methods taught by Euhus et al, wherein the details of said methods are taught by Pharmacia, Ljungquist, and Hofmann et al. It would have been obvious to use the ELISA detection methods taught by Euhus et al, wherein the details of said methods are taught by Exley et al, and the antibodies for detection are from autologous or alleogenic sera of melanoma

patients, as taught by Euhus et al, Rote et al, and Finck et al. It would have been obvious to combine the gel filtration, and DEAE purification methods taught by Euhus et al, with electrophoretic elution of UTAA from gel strips of SDS-PAGE, as taught by Hofmann et al, because of the following reasons: 1) Hofmann et al teach a combination of gel filtration, and SDS-PAGE gel elution methods for purifying a protein, wherein the SDS-PAGE step would further purify the protein from another protein, which is usually associated with the purified protein, and 2) Euhus et al teach that UTAA could be readily detected on SDS-PAGE, at molecular weights of 142 kD and 111 kD. The isolated UTAA, as taught by Euhus et al, would be the same as the claimed UTAA, which is isolated from urine and sera of melanoma patients, because urine and serum samples of melanoma patients could be used for UTAA isolation, wherein UTAA is originally found in urine of melanoma patients, and wherein the molecular weight (111 kD) of a subunit of UTAA taught by Euhus et al. is not significantly different from that of the claimed UTAA, having a molecular weight from about 90 kD to about 100 kD. Furthermore, the urine and serum samples of melanoma patients, that one of ordinary skill in the art could use for UTAA purification, would be the same as those used by applicant, because there is no specific teaching in the claims and the specification concerning any specific properties of urine and serum samples from melanoma patients which are used for UTAA purification.

Furthermore, UTAA isolated by the combination methods taught by Euhus et al, and Hofmann et al would be at least 95% or 99.5% free of immunoglobulin, because of the following reasons: 1) Euhus et al teach that the isolated UTAA is free of IgG and IgM, and 2) the gel slice

containing UTAA at a molecular weight of 111 kD would not contain immunoglobulin, which is well known in the art to have a molecular weight of about 150 kD. Although Euhus et al. do not specifically teach the degree of purification of UTAA, i.e at least at about 0.6% of total protein, and 105-fold over UTAA found in urine, such degree of purification is expected, given similar protocols used by Euhus et al and applicant, i.e. a UTAA fraction obtained from purification of urine by gel filtration. Once UTAA is isolated, it would have been obvious to dilute it or to concentrate it to various concentrations in a buffer.

In addtion, although Euhus et al do not teach that the isolated UTAA contains glycosidase-sensitive carbohydrates, is heat stable at 100^0 C and has an isoelectric point of about 6.1, however, the claimed UTAA appears to be the same as the prior art protein, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

It would have been obvious to use UTAA for inducing or enhancing the production of antibodies reactive to UTAA, because Euhus et al suggest the use of the isolated UTAA for the

immunoprognosis of human melanoma, and because it is well known in the art that tumor antigens are used for the production of antibodies, and antibodies to tumor are used for treating tumors (see for example, US 4,348,376). Furthermore, administering the same antigen UTAA is expected to give similar 2- to 5-fold enhancement in the production of antibodies reactive to UTAA, because the specification does not disclose any specific method of production of antibodies which is different from routine methods of production of any antibody known in the art.

One of ordinary skill in the art would have been motivated to isolate UTAA from urine of melanoma patients, and to use said isolated UTAA for inducing or enhancing the production of antibodies reactive to UTAA, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to isolate UTAA from urine of melanoma patients, and to use said isolated UTAA for inducing or enhancing the production of antibodies reactive to UTAA for the immunoprognosis of melanoma.

(11) Response to Argument

A. REJECTION UNDER 35 U.S.C. 101, OBVIOUSNESS-TYPE DOUBLE-PATENTING

In response to the rejection of claims 19, 62-66, 69-70, and 72-79 under 35 U.S.C. 101, obviousness-type double-patenting, Appellants intended to provide a terminal disclaimer. However, a terminal disclaimer has not been received by the Office. Rejection remains until a terminal disclaimer is received by the Office.

B. REJECTION UNDER 35 U.S.C. 112, SECOND PARAGRAPH

In response to the rejection of claims 19, 62, 65 and 73-79 under 35 U.S.C. 112, second paragraph, Appellants argue as follows:

Although usually there is no hard and fast rule as to what "substantial purity" means, in this case, however, there are a number of distinct indicators of what purity can be achieved in this system. For example, the present specification describes (a) UTAA protein that is purified about 100-fold and 105-fold over UTAA found in urine, (b) UTAA present as at least about 0.6% ot total protein in the composition; and (c) UTAA at about 95% and 99.5% free of immunoglobulin. Thus while each presenting distinct view of "substantial purity", these disparate characterizations all inform the skilled artisan of the metes and bounds of substantial purity.

Applicant's arguments have been considered but are not deemed to be persuasive for the following reasons:

The purity of the claimed UTAA in claims 19, 62, 65 and 73-79 are not limited to the degree of purity as recited in the specification. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, and would not know the metes and bounds of substantial purity.

C. REJECTION UNDER 35 U.S.C. 103

In response to the rejection of claims 19, 62-66, 69-70, and 72-79 under 35 U.S.C. 103, Appellants argue as follows:

The added reference by Hofmann et al in the most recent Office action is totally unrelated to the present application, and does not address the deficiencies of Euhus et al. Hofmann contribution at best is to provide a method of making UTAA, which is irrelevant as a matter of law. Appellants recite the case law of *in re Bell*, to argue that the issue is the obviousness of the claimed composition, not the method by which they were made.

Further, the primary reference, Euhus et al is not enabling, because the teachings of Euhus et al are not sufficient to permit one to reproducibly make and use the invention. Appellants recite the case law of *Paperless Accounting Inc. V. Bay area Rapid Transit Sys,* to argue that a reference must teach how to make and use the claimed invention.

The reference by Euhus et al at best provide an invitation to one of skill in the art to try the reproduce the invention. Appellants recite the case law of *In re O'Farrell*, to argue that "obvious to try" is not the standard for obviousness.

Appellants's arguments have been considered but are not deemed to be persuasive for the following reasons:

The Examiner acknowledges the recitation of the case law *in re Bell*, *Paperless Accounting Inc. V. Bay area Rapid Transit Sys* and *In re O'Farrell*. However, the case law *in re Bell*, concerning obviousness of the claimed composition, not the method by which they were made, is not relevant to the instant application, because a product by process is common in the art, and because as recited in the case law of *Paperless Accounting Inc. V. Bay area*

Rapid Transit Sys disclosed by Appellants, the references must teach how to make and use the claimed invention

Concerning the reference by Hofmann et al, Hofman et al would cure the deficiency of Euhus et al. Although Euhus et al teach that the purified antigen is free of IgM and IgG, and could be separated into two fractions of 142 kD and 111 kD under SDS-PAGE, Euhus et al do not teach that the purified antigen is 95% or 99.5% free of immunoglobulin. Hofmann et al teach a combination of gel filtration and SDS-PAGE gel slice elution for purifying a protein, wherein the SDS-PAGE step would further purify the protein from another protein, which is usually associated with the purified protein. Thus one of ordinary skill in the art would have expected that UTAA isolated by the combination methods taught by Euhus et al and Hofmann et al would be at least 95% or 99.5% free of immunoglobulin, because of the following reasons: The gel slice containing UTAA at a molecular weight of 111kD would not contain immunoglobulin, which is well known in the art to have a molecular weight of about 150 kD. In addition, the specification does not disclose any purification of UTAA from Ig's other than IgG and IgM, and the claims do not specify that UTAA is 95% or 99.5% free of Ig's other than IgG and IgM.

Concerning the enablement of the primary reference by Euhus et al, the case law of *Paperless Accounting Inc. V. Bay area Rapid Transit Sys* does not apply to the reference by Euhus et al. Euhus et al teach isolation of UTAA, which has the same following properties as the claimed UTAA: 1) similar to the claimed UTAA, UTAA taught by Euhus et al is from

sera or urine of melanoma patients, and 2) UTAA taught by Euhus et al has a molecular weight at about 111kD under SDS-PAGE, which is not significantly different from the molecular weight of about 90 to 100 kD under SDS-PAGE of the claimed UTAA. Further, similar to the disclosure of the specification (see Example 1, isolation of UTAA from urine, in specification, pages 22-23, and Example XI, isolation of UTAA from serum, in specification, pages 33-34), Euhus et al teach that UTAA is free of IgG and IgM, and could be isolated by gel filtration, and DEAE anion exchange chromatography, and detected using autologous or allogenic antibody in ELISA. Although Euhus et al do not teach in details how to perform ELISA, gel filtration and DEAE anion exchange chromatography, such techniques are routine in the art, and are provided by the secondary references.

Thus the case law *In re O'Farrell* concerning "obivous to try' does not apply to the instant application, because with a combination of the methods taught by Euhus et al and the secondary references, one of ordinary skill in the art would have expected to obtain a protein with the same properties as the claimed UTAA, and having the same degree of purity.

The followings are more in details of the arguments against the rejection.

1. Parameters necessary for the isolation of UTAA from urine

Appellants argue as follows:

Assuming one could isolate some fraction containing UTAA, how would one know that they had purified the correct antigen, much less identify a patient that even contained these

substances? The prior art fails to teach which fraction contained UTAA, or how one could indentify UTAA from any other protein, using any readily obtainable, well-characterized antibodies.

Appellants's arguments have been considered but are not deemed to be persuasive for the following reasons:

It is not necessary to use well-characterized antibodies, such as monoclonal antibodies to UTAA, to identify UTAA purified from urine or sera of melanoma patients, because Euhus et al teach that UTAA could be detected by ELISA using autologous or allogenic antibodies, i.e. antibodies specific for UTAA from sera from melanoma patients. ELISA is routine in the art, the details of said method is taught by Exley et al. Further, autologous sera has been used for detection of tumor associated antigens found in urine of patients, as taught by Rote et al, and Finck et al. Although in patient sera, there are several antibodies reacting to proteins other than UTAA, UTAA could be differentiated from other proteins by detecting a protein having a molecular weight of 110 kD under SDS-PAGE that reacts with the patient sera. In other words, fractions eluted from gel filtration or DEAE column could be readily identified by SDS-PAGE, immunoblotted and detected with patient sera, wherein a positive fraction is a fraction that has a protein at 110 kD which reacts positively with patient sera.

2. Structure and immunologic profile of UTAA

Appellants argue as follows:

While there is no disclosure of an amino acid sequence of UTAA, the present application contains considerably more information with regard to how one goes about purifying UTAA, not about purifying proteins generally. Further, one would not know how to detemine whether a given serum would bind to UTAA as opposed to some other antigen? To the contrary, the skilled artisan could use the antibody disclosed in the present application to identify UTAA.

Appellants's arguments have been considered but are not deemed to be persuasive for the following reasons:

One of ordinary skill in the art could obtain a protein which has the same properties as the claimed UTAA, with the same expected degree of purity, using the information from the recited references, mainly gel filtration and DEAE exchange chromatography of urine or sera from melanoma patients, as taught by Euhus et al, wherein the details of said methods are taught by Pharmacia, Ljungquist, and Hofmann et al, and further purification by gel slice elution as taught Hofmann et al. For detection, autologous or allogenic antibodies from sera of melanoma patients could be used in ELISA, as taught by Euhus et al, wherein the details of said methods are taught by Exley et al, Rote et al, and Finck et al. Fractions eluted from gel filtration or DEAE column could be readily identified by SDS-PAGE, immunobloted and detected with patient sera, wherein a positive fraction is a fraction that has a protein at 110 kD which reacts positively with patient sera.

3. The Reisfield Declaration

Appellants submitted a Declaration by Dr. Reisfield, reciting that key conditions such as the proper pH or ionic strength under which isolation was conducted was missing in the Euhus reference. Thus one could not reproducibly isolate and purify UTAA.

Appellants further submitted a second Declaration by Dr.Reisfield, reciting that 1) the Euhus reference does not contain information on the sequence of UTAA, and 2) although Euhus et al recite a murine antibody that binds to UTAA, this antibody is neither described nor was it publicly available at the time the invention was made. Thus reproduction of the work described in Euhus et al abstract would have lack a reasonable expectation of success. Even if one would have fortuitously reproduced the work described in Euhus et al, one could not have confirmed such a success with the information available.

Appellants's arguments have been considered but are not deemed to be persuasive for the following reasons:

Specific pH or ionic strength is not required, because such conditions apply only to step elution of a protein in a DEAE chromatography. It is well known in the art that a protein could be isolated with a gradient elution using a range of salt or pH concentrations, as taught by Pharmacia, Ion exchange chromatography (see in particular figure 23, p.45, and figure 24, p.46). Fractions eluted from gel filtration or DEAE column could be readily identified by SDS-PAGE and detection with patient sera, wherein a positive fraction is a fraction that has a protein at 110 kD which reacts positively with patient sera, *supra*.

Concerning the second Declaration by by Dr.Reisfield, the specification nor the claims recite the sequence of UTAA. Further, a well characterized antibody specific for UTAA is not necessary for detection of UTAA, as discussed above, under section 1) Parameters necessary for the isolation of UTAA from urine.

4. The Shively Declaration

Appellants also submitted a Declaration by Dr. Shively, stating the followings: 1) UTAA was usually isolated as an antigen-antibody complex in a fraction containing other antibody complexes. Such an unfractionated complex must contain many other antibodies and proteins irrelevant to UTAA. Further, some sera are free of immune complexes, but insufficient information was given on how to identify such sera, or how to modify the isolation procedure to successfully isolate the antigen under these distinct circumstances, and 2) While it is correct that molecular masses reported from SDS gel are often in error by 10%, it also is true that this potential error leads to a source of confusion in the identification of proteins. The specific details of a given protein purification are critical to the establishment of identity of a protein. In this case, the Euhus abstract was only a preliminary report.

Appellants again conclude that the Euhus abstract cannot be considered to provide the essential "enabling methodologies" or the "reasonable likelihood of success" that are required for a *prima facia* case of obviousness.

Appellants's arguments have been considered but are not deemed to be persuasive for the following reasons:

Nowhere in the specification do Appellants disclose the identification of sera that are free of immune complex for use in the purification of UTAA, or the modification of the isolation procedure to isolate UTAA under these circumstances. In other words, the urine or sera sample used for purification of UTAA as disclosed by the specification is not different from the sera or urine samples taught by Euhus et al, Rote et al, or Finck et al. Further, although Euhus et al teach that UTAA is circulated in melanoma patients as immune complexes containing IgG and IgM, Euhus et al also teach that the isolated UTAA is free of IgG and IgM.

In addition, discussion concerning details of purification has been set forth under section 3) The Reisfield Declaration. Further, this is a 103 rejection, wherein the combined references are considered, and not the primary reference by Euhus et al alone.

5. Individual teachings of the secondary references

Appellants argue as follows:

The secondary references merely constitute generally related background methodologies. The only disclosures that bear upon UTAA are the teaching by Rot et al and Finck et al, which only establish that the described antigens are heat stable to 100^0C, a fact that can hardly be said to remedy the problem of reproducibility. None of these references disclose the structure of UTAA or how to isolate UTAA. Appellants again emphasize that the claims are drawn to a unique tumor antigen, not to methods by which such antigen hypothetically could be produced.

Appellants's arguments have been considered but are not deemed to be persuasive for the following reasons:

The secondary references are recited to teach more in details the routine methods for purification of UTAA as taught by Euhus et al. Further, Hofman et al would cure the deficiency of Euhus et al. Although Euhus et al teach that the purified antigen is free of IgM and IgG, and could be separated into two fractions of 142 kD and 111 kD under SDS-PAGE, Euhus et al do not teach that the purified antigen is 95% or 99.5% free of immunoglobulin. Hofmann et al teach a combination of gel filtration and SDS-PAGE gel slice elution for purifying a protein, wherein the SDS-PAGE step would further purify the protein from another protein, which is usually associated with the purified protein. Thus one of ordinary skill in the art would have expected that UTAA isolated by the combination methods taught by Euhus et al and Hofmann et al would be at least 95% or 99.5% free of immunoglobulin, because of the following reasons: The gel slice containing UTAA at a molecular weight of 111kD would not contain immunoglobulin, which is well known in the art to have a molecular weight of about 150 kD.

Moreover, the secondary references are recited to teach more in details the purification steps taught by Euhus et al, i.e. how to make the claimed UTAA, wherein the details of the purification, i.e. specific details of protein purification, are critical to the establishment of identity of a protein, as recited by Appellants in the Shively Declaration. Further, as recited in

the case law of *Paperless Accounting Inc. V. Bay area Rapid Transit Sys* disclosed by Appellants, the references must teach how to make and use the claimed invention

6. Claims 63, 64, 66, 69 and 70 are separately patentable

Appellants argue as follows:

Claims 63, 64, 66, 69 and 70 are drawn to various levels of UTAA purity. The Examiner argues that in view of similar treatment of UTAA by Euhus and Appellants, that the values were achieved. This is arguing inherency, which has no place in an obviousness analysis. Appellants recite *In re Spormann* to support this inherency argument. Further, although Euhus et al teach that the sample was IgM and IgG free, Euhus reports nothing regarding other immunoglobulin species-there could have been 1-6% contamination with other Ig's. This issue is not addressed by the references nor by the Examiner.

Appellants's arguments have been considered but are not deemed to be persuasive for the following reasons:

The Examiner acknowledges the recitation of the case law *In re Spormann*. However, the case law *In re Spormann* does not apply to the instant application.

Example 1, pages 22-23 in the specification, discloses that after gel filtration of a urine sample of a melanoma patient, UTAA as detected by allogenic antibody is present as 0.6% of total protein, and is purified 105-fold over UTAA found in urine. Example XI, pages 33-34 in the specification, discloses that after DEAE chromatography of melanoma serum, UTAA is detected in second peak, which is contaminated with a small amount of IgG. Said

contaminated IgG is removed by further absorption with anti-human IgG immunobeads, resulting in UTAA which is 95% or 99.5% free of IgG.

Although Euhus et al do not specifically teach the degree of purity of the isolated UTAA, i.e. present as 0.6% of total protein, and is purified 105-fold over UTAA found in urine, one of ordinary skill in the art would have expected that after gel filtration, as taught by Euhus et al, a urine sample from a melanoma patient would yield the same UTAA with the same degree of purity as the claimed UTAA, since the urine samples taught by Euhus et al are the same as the claimed urine samples, and the protocol of purification is the same, i.e. gel filtration. Further, as discussed in the Office action of paper No: 73, on 06/21/00, the specification does not disclose any purification of UTAA from Ig's other than IgG and IgM, and the claims do not specify that UTAA is 95%-99.5% free from Ig's other than IgG and IgM. Thus purification from Ig's other than IgG and IgM is not an issue for 103 rejection here. Moreover, one of ordinary skill in the art would have expected that UTAA isolated by the combination methods tuaght by Euhus et al and Hofmann et al would be at least 95% or 99.5% free of immunoglobulin, because of the following reasons: The gel slice containing UTAA at a molecular weight of 111kD would not contain immunoglobulin, which is well known in the art to have a molecular weight of about 150 kD.

In summary, UTAA isolated by one of ordinary skill in the art, using urine or serum from melanoma patients, and the combined methods taught by prior art, would be the same as the claimed UTAA, for the following reasons: 1) Both proteins are derived from the same

sources, i.e. urine or serum from melanoma patients, 2) The samples are purified by the same gel filtration and DEAE methods, except for gel slice elution for further purification, and 3) Both proteins have similar molecular weight under SDS-PAGE and could be detected with autologuous or allogenic antibodies from sera of melanoma patients.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Patent Examiner,

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